REMARKS

Claims 1-8 are pending in the present application. Claims 1-7 are rejected. Claims 1-3 are herein amended. New claims 11-14 are added herein.

Applicants' Response to Claim Rejections under 35 U.S.C. §112

Claims 1-7 were rejected under 35 U.S.C. §112, first paragraph, as failing to comply with the written description requirement.

The Office Action states that the polypeptide (P) comprises at least one species of peptide (X) and an auxiliary amino acid sequence (Y). The Office Action states that the polypeptide (P) as recited in the claim represents "any and all peptides that comprises of the peptide (X) and peptide (Y)." The Office Action appears to complain that the structure of (Y) and the nature of the association between (X) and (Y) are not disclosed.

Polypeptide (P)

The Office Action refers to ProNectin F and concludes that "the molecular weight disclosed for each of these ProNectins indicates that the polypeptide in each case is not just limited to the composition of the peptides (X) and (Y) and contains unknown structural features that is neither well defined in the specification nor recited in the claims." Based on an average molecular weight of ~110 daltons, the Office Action calculates that the molecular weight of ProNectin F should be ~81,510 d. However, as the Office Action notes, the disclosed molecular weight of ProNectin F is ~110,000 d. Thus, the Office Action concludes that there is a

discrepancy in the molecular weight of the disclosed sequence and the actual molecular weight of the polypeptide which is the result of alleged "unknown structural features."

In response to this point, Applicants respectfully note that according to Sanyo Chemical Industries, the sequence of ProNectin F is as disclosed in the specification, without any "unknown structural features." Sanyo's product specification webpage (http://www.sanyo-chemical.co.jp/product/pronectin/eng/prodspec.htm) explains as follows:

> Based on its gene sequence, ProNectin® F is a protein of 72,738 daltons. As determined by SDS-PAGE, using soluble proteins as molecular weight standards, the approximate apparent molecular weight is 110,000. Differences are due to the unusual amino acid composition of the protein.

Thus, the assumption that "unknown structural features" are present is improper. In order to assist the Examiner, Applicants herewith submit a copy of this product specification. In this production specification, the molecular weight measured by the SDS-PAGE method and the molecular weight with the unit "daltons" are described. The molecular weight with the unit "daltons" differs from both the molecular weight measured by the SDS-PAGE method and the calculated molecular weight assumed by the Office Action. However, there is no contradiction between these values, for the reasons discussed below.

Each amino acid has a specific, different molecular weight. Therefore, it is meaningless to calculate a molecular weight of a polypeptide by using an assumed average molecular weight of amino acids. Moreover, in the present invention, the weight average molecular weight (Mw) of the polypeptide (P) is measured by the SDS-PAGE method. Applicants note that the specification provides a clear explanation:

> In the context of the present invention, the weight average molecular weight (Mw) of the polypeptide (P) is determined by the method which comprises fractionating a sample (e.g. polypeptide and the like) by SDS-PAGE (SDS-polyacrylamide gel electrophoresis) and comparing the migration distance thereof with that of the standard substance. Page 8, lines 28-34.

Thus, Mw is without a unit, such as "daltons." In other words, the Mw of the polypeptide (P) in the present invention is not calculated from the molecular weight of each amino acid. Accordingly, the Mw of the polypeptide may be different from the calculated molecular weight assumed in the Office Action. Therefore, Applicants respectfully submit that there is no discrepancy, and there are no alleged "unknown structural features" present. Thus, the claims comply fully with the written description requirement

Minimum Molecular Weight

The Office Action goes on to state that the specification discloses a peptide having a molecular weight between 1,000 and 1,000,000. Further, Applicants respectfully note the misquotation at page 10, lines 17-20. This passage misquotes page 24 of the specification as stating that ProNectin F "...has a Mw of about *110,000 d*." Rather, this passage of the specification states that ProNectin F "...has a Mw of about *110,000*." Please see page 24, line 22 and note the absence of the unit "d."

As noted above, this molecular weight is without units, and is measured by SDS-PAGE, not by calculation of amino acid sequence. Based on the Office Action's calculations, the minimum number of residues is 9 and the maximum number of residues is 9090. The Office Action then states that "[i]f the polypeptide (P) has a structure that has (X) and (Y) peptide

moieties bonded to each other in an alternating fashion (according to claim 4), then a minimum molecular of 1000 d for the polypeptide (P) is irrelevant because, such a peptide comprising minimum 3 of peptide (X) and minimum 2 of peptide (Y) is not possible as it would exceed the minimum molecular weight limitations disclosed in the specification as per the recited claims." Page 11.

Applicants respectfully submit that the logic of the Office Action is unclear. However, it appears that the Office Action intends to state that the shortest possible polypeptide would have a greater molecular weight than the disclosed minimum molecular weight of 1000. Accordingly, it is unclear why the claims would be rejected as indefinite based on this point. In other words, if the shortest possible polypeptide was less than the minimum molecular weight of 1000, the rejection may be clear. However, this is not the case. Accordingly, the Examiner is respectfully requested to clarify this point.

Content of the Polypeptide

Finally, with respect to claim 1, the Office Action states that "if the peptides represent 'any peptide sequence', then there are 9^{20} sequences for the minimum molecular weight and 9090^{20} sequences for the molecular weight 1,000,000 comprising only the 20 naturally occurring amino acid residues."

Again, the logic of the Office Action is unclear. Applicants respectfully submit that the claims do not recite "any peptide sequence" having a molecular weight between 1,000 and

1,000,000. Rather, the claims specifically recite specific amino acid sequence for amino acid sequence (X). Accordingly, the Examiner is respectfully requested to clarify this point.

Summary

With respect to claim 1, in summary, Applicants respectfully submit that the Office Action's logic is not entirely clear and illustrates a lack of recognition of the difference between molecular weight based on amino acid sequence and molecular weight based on SDS-PAGE. However, in order to further clarify the claimed subject matter, Applicants herein amend claim 1 in order to further define the structure of polypeptide (P).

Specifically, Applicants herein amend claim 1 in order to more specifically recite the structure of the auxiliary sequence (Y). Please see amended claim 1 and new claims 11 and 12. These amendments are supported at least by page 4, line 18 to page 5, line 15. Additionally, amended claim 1 recites that "at least one" auxiliary sequence (Y) may be used. This is supported at least by page 7, lines 29-31. Similarly, amended claim 1 recites that "at least one" polypeptide (P) may used. This is supported at least by page 10, lines 1 and 2. Applicants respectfully submit that these claim amendments are sufficient to overcome the pending rejections with respect to written description.

Claims 2 and 3

Applicants now discuss claims 2 and 3. With respect to claim 2, the Office Action states that "[i]t is unclear from the recitation whether the number 3 to 50 represents the number of

repeat units of the polypeptide (X) or it is the length of the polypeptide sequence." The Office Action states that if this number means the length of the peptide sequence with a repeated RGD, then a length other than a multiple of 3 does not have adequate support. The Office Action makes a similar rejection to claim 3.

Claims 2 and 3 are intended to recite that the amino acid sequences (X) and (Y) are repeated 3 to 50 and 2 to 51 times, respectively, in the polypeptide. Accordingly, Applicants herein amend claims 2 and 3 in order to improve their clarity. Favorable reconsideration is respectfully requested.

New Claims 13 and 14

Additionally, Applicants herein add new claims 13 and 14. Claim 13 recites that the at least one polypeptide (P) is selected from the group consisting of ProNectin F, ProNectin F2, ProNectin F3, ProNectin L, ProNectin L2, ProNectin L3, ProNectin Y, ProNectin Y2 and ProNectin Y3. Claim 14 further recites that the at least one polypeptide (P) is selected from the group consisting of ProNectin F and ProNectin L. These amendments are supported at least by page 8, line 35 to page 9, line 35.

Applicants note that the polypeptide (P) defined in claim 1 includes these recited ProNectins. For example, ProNectin F has Arg-Gly-Asp (SEQ ID NO: 3) as the minimal amino acid sequence (X), repeated 13 times. ProNectin F also has $(Gly\text{-}Ala\text{-}Gly\text{-}Ala\text{-}Gly\text{-}Ser)_9$ (residues 1-6 of SEQ ID NO: 7) as auxiliary amino acid sequence (Y), repeated 13 times. These

(X) and (Y) sequences are bonded together in an alternating fashion. See page 9, lines 4-11. Favorable consideration is respectfully requested.

Claims 2 and 3 were rejected under 35 U.S.C. §112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Similar to the rejection based on 35 U.S.C. §112, first paragraph, above, with respect to claim 2, the Office Action states that "[i]t is unclear from the recitation whether the number 3 to 50 represents the number of repeat units of the polypeptide (X) or it is the length of the polypeptide sequence." The Office Action states that if this number means the length of the peptide sequence with a repeated RGD, then a length other than a multiple of 3 does not have adequate support. The Office Action makes a similar rejection to claim 3.

In response, Applicants respectfully submit that the amendments to claims 2 and 3, discussed above, are sufficient to overcome this rejection. Favorable reconsideration is respectfully requested.

Applicants' Response to Claim Rejections under 35 U.S.C. §103

Claims 1-7 were rejected under 35 U.S.C. §103(a) as being unpatentable over Ferrari et al. (U.S. Patent No. 6,184,348) in view of Cook et al. (U.S. Patent No. 5,916,585).

It is the position of the Office Action that Ferrari discloses the invention as claimed, with the exception of (1) the use of polyalkylenepolyamine or polyarylenepolyamine matrices and (2)

covalent bonding between the peptide and the polymer sheet. The Office Action relies on Cook to provide the teaching of the use of polyalkylenepolyamine or polyarylenepolyamine matrices. The Office Action alleges that it would have been obvious to attach the polypeptide to the polymer sheet by covalent bonding.

In the Office Action dated July 12, 2007, the Office Action stated that then-pending claim 10 would be allowable if rewritten in independent form. In other words, the Office Action acknowledged that claim 10's recitation of covalent bonding between the polypeptide and the sheet was not disclosed or suggested by the cited art.

However, the Office Action now alleges that it would have been obvious to modify the combination of Ferrari and Cook by covalently bonding the polypeptide and the sheet. The Office Action bases this position on the recent *KSR* Supreme Court decision. In view of the limited number of methodologies to attach the polymer and the sheet (i.e., ionic interaction, hydrophobic interaction, physical adsorption, reversible cross-linking and covalent bonding), the Office Action alleges that it would have been "obvious to try" covalent bonding.

However, Applicants respectfully submit that the Office Action's reliance on *KSR* is misplaced. "The *KSR* opinion only focused on the Federal Circuit's strict use of the TSM test in performing the obviousness analysis; it did not mention or affect the requirement that each and every claim limitation be found present in the combination of the prior art references before the analysis proceeds." *Abbott Labs v. Sandoz, Inc.*, 500 F. Supp. 2d 846, 852 (D. Ill. 2007). As further explained in *Abbott Labs v. Sandoz*, "[i]n the *KSR* opinion, the Court mentioned two Federal Circuit opinions in which the Courts utilized broader, more flexible versions of the TSM

test. 127 S. Ct. at 1743. In one of those opinions, the Federal Circuit again instructed that before inquiry into the teaching or motivation of the prior art, all claim limitations must be found in the prior art references. DyStar Textilfarben GmbH & Co. Deutschland KG v. C.H. Patrick Co., 464 F.3d 1356, 1360 (Fed. Cir. 2006)." *Id* (emphasis added).

In other words, without a showing that all claim limitations have been found in the prior art, the Office Action's remarks regarding *KSR* are not relevant. Therefore, since the Office Action has not provided a showing of art which teaches that "the polypeptide (P) and the sheet (S) are bonded by a covalent bonding," Applicants respectfully submit that *prima facie* obviousness has not been established. Therefore, Applicants respectfully submit that the rejection is improper and should be withdrawn.

Additionally, Applicants provide the following comments with respect to reasons why it would not have been obvious to combine the teachings of Ferrari and Cook, aside from the issue of a covalent bonding, discussed above.

The claimed invention relates to a wound dressing for accelerating epidermal regeneration which comprises a polypeptide (P) having at least one species of epidermal regeneration-accelerating minimal amino acid sequences (X) selected from the group consisting of Arg-Gly-Asp (SEQ ID NO: 1), Ile-Lys-Val-Ala-Val (SEQ ID NO: 2), and Tyr-Ile-Gly-Ser-Arg (SEQ ID NO: 3) and at least one auxiliary amino acid sequence (Y); a polyalkylenepolyamine and/or polyarylenepolyamine (A) having a Mw of 2,000 to 60,000; and a sheet (S) being polyurethane; wherein the polypeptide (P) and the sheet (S) are bonded by a covalent bonding.

The wound dressing of the present invention has an extremely high epidermal regeneration accelerating effect by the above constitution, namely by using the specific polypeptide (P), the specific polyalkylenepolyamine and/or polyarylenepolyamine (A) and the specific sheet (S), wherein the polypeptide (P) and the sheet (S) are bonded by a covalent bonding. Therefore, the wound dressing of the present invention is suited for the therapy of defected skin wounds and can treat wounds without burdens on patients.

On the other hand, Ferrari relates to a recombinantly produced proteinaceous polymer composition. As the Office Action recognizes, Ferrari does not teach the use of a polyalkylenepolyamine and/or polyarylenepolyamine. Moreover, Ferrari describes "the subject material may be made into or coated on woven fabrics, films or membranes," as the Office Action mentions. However, Ferrari does not describe the kinds of films or membranes or even suggest polyurethane as a sheet. Furthermore, as the Office Action recognizes, Ferrari does not disclose that a polypeptide and a sheet are bonded by a covalent bonding. In addition, Ferrari does not disclose that acceleration of epidermal regeneration and rapid cure of wounds can be obtained by using the wound dressing of the present invention having the above specific constitution.

Cook relates to a biodegradable material for immobilization of a bioactive species thereon, the material comprising a porous hydrophobic biodegradable support member and a first layer comprised of at least one species of a polymeric surfactant, and wherein the surfactant is cross-linked to itself with a cross-linking agent. Cook discloses that the bioactive species are immobilized directly to chemical functional groups of the first layer as shown in the Figures.

Namely, the bioactive species are immobilized not to the hydrophobic support member, but to the first layer comprised of the surfactant. Thus, as the Office Action recognizes, Cook does not disclose that the bioactive species and the hydrophobic support member are bonded by a covalent bonding. In addition, Cook does not disclose that the acceleration of epidermal regeneration and rapid cure of wounds can be obtained by using the wound dressing of the present invention having the above specific constitution.

Accordingly, even if Ferrari, which does not disclose polyalkylenepolyamine and/or polyarylenepolyamine, and Cook, which does not immobilize the bioactive species directly to the hydrophobic support member, are combined, the combination neither discloses nor suggests the wound dressing of the present invention comprising the specific polypeptide (P), the specific polyalkylenepolyamine and/or polyarylenepolyamine (A) and the specific sheet (S), wherein the polypeptide (P) and the sheet (S) are bonded by a covalent bonding.

Furthermore, the combination of cited art does not disclose or suggest that the above excellent effects (acceleration of epidermal regeneration and rapid cure of wounds) can be obtained by using the wound dressing of the present invention having the above specific constitution. Therefore, the covalent bonding of the peptide with the matrix is not "the product of innovation but of ordinary skill and common sense" as alleged by the Office Action. Consequently, the claimed embodiments are not disclosed by the combination of cited art. Further, the claimed embodiments would not have been obvious to one having ordinary skill in the art in view of the cited references. Favorable reconsideration is respectfully requested.

For at least the foregoing reasons, the claimed invention distinguishes over the cited art and defines patentable subject matter. Favorable reconsideration is earnestly solicited.

Should the Examiner deem that any further action by applicants would be desirable to place the application in condition for allowance, the Examiner is encouraged to telephone applicants' undersigned attorney.

If this paper is not timely filed, Applicants respectfully petition for an appropriate extension of time. The fees for such an extension or any other fees that may be due with respect to this paper may be charged to Deposit Account No. 50-2866.

Respectfully submitted,

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RBC/nrp
Enclosure: Sanyo Product Specification Sheet for ProNectin

Cell Culture Products

Sanyo Chemical Industries, Ltd.

Product Specifications

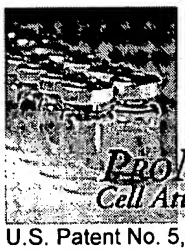
PRONECTIN® F
Cell Attachment Factor

PRONECTIN® F PLUS
Cell Attachment Factor

U.S. Patent No. 5,514,581 and other patents pending

Product Specifications

Description:	ProNectin® F is a protein polymer, produced from a synthetic gene via bacterial fermentation, which presents multiple copies of the RGD cell attachment sequence from human fibronectin.
Molecular Weight:	Based on its gene sequence, ProNectin® F is a protein of 72,738 daltons. As determined by SDS-PAGE, using soluble proteins as molecular weight standards, the approximate apparent molecular weight is 110,000. Differences are due to the unusual amino acid composition of the protein.
Activity:	Tested for the promotion of adherence of VERO cells.
Leachable Endotoxins:	Leachable endotoxins must be $\leq$ 0.250 EU/ml for the lot to pass Quality Assurance.
Sterility:	The final product is tested according to USP Chapter 71. Samples tested must show the lot to have no bacterial, fungal, or yeast growth after 14 days.
Stability:	Storage tests indicate that the protein powder and coated substrates retain their performance for at least 2 years at room temperature.
Diluent:	Lithium perchlorate solution ($LiClO_4$, 4.5 molar). Contains $\leq$ 5 ppm heavy metals as specified by manufacturer. No detectable influence on seeded cells has been observed when the protocol for use is followed.



U.S. Patent No. 5,514,581 and other patents pending

Product Specifications

Description: ProNectin® F Plus is a water-soluble protein polymer which exhibits multiple copies of the RGD cell attachment sequence from human fibronectin and has a net positive charge.

All other Product Specifications are the same as described for ProNectin® F.

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